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CA15-3 and alkaline phosphatase as predictors for breast cancer recurrence: a combined analysis of seven International Breast Cancer Study Group trials

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For the International Breast Cancer Study Group

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Background: We evaluated the ability of CA15-3 and alkaline phosphatase (ALP) to predict breast cancer recurrence.

Patients and methods: Data from seven International Breast Cancer Study Group trials were combined. The primary end point was relapse-free survival (RFS) (time from randomization to first breast cancer recurrence), and analyses included 3953 patients with one or more CA15-3 and ALP measurement during their RFS period. CA15-3 was considered abnormal if >30 U/ml or >50% higher than the first value recorded; ALP was recorded as normal, abnormal, or equivocal. Cox proportional hazards models with a time-varying indicator for abnormal CA15-3 and/or ALP were utilized.

Results: Overall, 784 patients (20%) had a recurrence, before which 274 (35%) had one or more abnormal CA15-3 and 35 (4%) had one or more abnormal ALP. Risk of recurrence increased by 30% for patients with abnormal CA15-3 [hazard ratio (HR) = 1.30; $P = 0.0005$], and by 4% for those with abnormal ALP (HR = 1.04; $P = 0.82$). Recurrence risk was greatest for patients with either (HR = 2.40; $P < 0.0001$) and with both (HR = 4.69; $P < 0.0001$) biomarkers abnormal. ALP better predicted liver recurrence.

Conclusions: CA15-3 was better able to predict breast cancer recurrence than ALP, but use of both biomarkers together provided a better early indicator of recurrence. Whether routine use of these biomarkers improves overall survival remains an open question.

Key words: alkaline phosphatase, breast cancer, CA15-3, tumor marker

introduction

CA15-3 is a mucin belonging to a large family of glycoproteins encoded by the *MUC 1* gene [1] that are heterogeneously expressed on the apical surface of normal epithelial cell types, including those of the breast [2]. CA15-3 is elevated in a proportion of breast cancer patients with distant metastases. Though current American Society of Clinical Oncology [3] and National Comprehensive Cancer Network [4] guidelines do not recommend its use for surveillance purposes, elevated CA15-3 is used to anticipate detection of recurrences in patients with breast cancer [5], and as an additional tool in evaluating therapeutic response of advanced disease [6]. Preoperative levels of CA15-3 have a significant and independent relation to outcome in patients with early breast cancer. Patients with high concentrations have a significantly worse prognosis than those with low concentrations, both in terms of disease-free survival and overall survival (OS) [5, 7–11], probably due to a larger burden of occult disease. CA15-3 measured during follow-up has been consistently shown to predict liver and bone metastases [12]. This is biologically plausible, since in many adenocarcinomas, mucins are aberrantly overexpressed throughout the cytoplasm and on the cell surface in an

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underglycosylated form, and then shed into the circulation [13–15]. Disease progression can therefore be accompanied by increased presence of large glycoproteins in the serum [16]. CA15-3 has been shown to be an independent predictor of first recurrence in multivariate analyses, and a powerful prognostic indicator in patients with advanced breast cancer [17], but its role in monitoring patients with no overt disease has not been established [18–20].

Alkaline phosphatase (ALP) is a serum enzyme whose total levels reflect the combined activity of several isoenzymes found in the liver, bone, kidney, and intestinal lining. The skeletal isoenzyme originates in osteoblasts that release large amounts of the enzyme when bone repair activity occurs, for example with bone metastases. In cancer patients, ALP is a sensitive indicator of mild biliary obstruction, thus being a very sensitive indicator of liver progression. In a study conducted by the International Breast Cancer Study Group (IBCSG), ALP, aspartate transaminase (AST) and γ-glutamyltransferase (GGT) were examined for their sensitivity in detecting breast cancer recurrence. ALP alone was abnormal in a high proportion of breast cancer patients with bone metastases and/or liver metastases, and was more effective than AST and GGT in distinguishing patients with relapse from those without [21].

In this retrospective analysis, we evaluate the ability of CA15-3 and ALP to predict breast cancer recurrence when used alone and in combination.

patients and methods

patients

A total of 5961 eligible patients entered IBCSG trials VIII [22] and IX [23], and trials 11–15 [24–27] from 1988 to 2000. At the time of the present analysis, all patients had completed their primary treatment. Table 1 summarizes the trials included in the analysis. Informed consent was required according to the criteria established within individual countries. The trial protocols were reviewed and approved by local institutional review boards.

Clinical, hematological, and biochemical assessments for each patient were required every 3 months for the first year, every 6 months for the second year, and yearly thereafter. Assessments included ALP, aspartate aminotransferase, GGT, bilirubin, calcium, and creatinine, which were recorded on the forms as normal, abnormal, or equivocal. The measurement of CA15-3 (U/ml) was optional, but strongly encouraged at yearly intervals. Mammography of the contralateral breast (and conserved breast, if applicable) was carried out yearly. All study records (initial data, treatment, toxicity, and recurrence) were reviewed centrally by the data management and medical staff.

The primary outcome was relapse-free survival (RFS), defined as the time from randomization to the first breast cancer recurrence, not including

Table 1. Descriptions of IBCSG trials

IBCSG Trial	Patient population	Years accrual	Eligible patients	Treatments	Median follow-up (years)
VIII	Premenopausal N−	1990–1999	1109	Observation versus Goserelin versus CMF × 6 versus CMF × 6 → Goserelin	8.0
IX	Postmenopausal N−	1988–1999	1669	Tam versus CMF × 3 → Tam	8.9
11–93	Premenopausal (ER/PgR ≥ 10), suitable for ET alone	1993–1998	174	OFS → Tam versus OFS → AC × 4 → Tam	7.2
12–93	Postmenopausal (ER ≥ 10), suitable for ET alone	1993–1999	450	Tam versus Tor	5.9
13–93	Premenopausal	1993–1999	1246	AC × 4 → CMF × 3 versus AC × 4 → Gap → CMFx3 versus AC × 4 → CMF × 3 → Tam versus AC × 4 → Gap → CMF × 3 → Tam	6.3
	Not suitable for ET alone				
14–93	Postmenopausal, not suitable for ET alone	1993–1999	969	AC × 4 → CMF × 3 → Tam/Tor versus AC × 4 → Gap → CMF × 3 → Tam/Tor	6.9
15–95	High risk	1995–2000	344	EC/AC × 4 → CMF × 3 → Tam versus Dose Intensive EC × 3 → Tam	4.8
Overall			5961		6.7

IBCSG, International Breast Cancer Study Group; N−, node negative; CMF, cyclophosphamide, methotrexate, fluorouracil; ER, estrogen receptor; PgR, progesterone receptor; ET, endocrine therapy; OFS, ovarian function suppression; Tam, tamoxifen; AC, adriamycin, cyclophosphamide; Tor, toremifene; EC, epirubicin, cyclophosphamide.

second nonbreast malignancies. Secondary end points included time to first bone recurrence, time to first liver recurrence, and time to first nonliver visceral recurrence. Elevated CA15-3 and/or ALP levels were not defined in the protocol as criteria for defining recurrence.

CA15-3 values (assessed locally) were classified as abnormal if >30 U/ml or if >50% greater than the first CA15-3 value recorded for the patient. The cut-off of 30 U/ml was determined before looking at the data and was chosen to be consistent with other studies [5, 8, 10, 17, 28]. Only patients who had both CA15-3 and ALP measured at least once any time during their RFS period (i.e. before first recurrence, or before last follow-up visit if no recurrence) were included in the analyses.

statistical analyses

All analyses were generated for CA15-3 alone, ALP alone, and for CA15-3 and ALP used together (either abnormal and both abnormal). A Cox proportional hazards regression model was fit with RFS as the outcome and a time-varying indicator for whether or not the biomarkers were abnormal as the covariate. For a fixed time point t (where $t <$ RFS time), the time-varying indicator was assigned a value of one if one or more measurement up to time t was abnormal, and a value of zero if all measurements up to time t were normal. Time-varying Cox model analyses were generated in lieu of sensitivity-type analyses to take into account the time to event, and to ensure that patients with similar follow-up time were compared in the analyses. Cox model analyses were also generated for each of the secondary end points. Analyses were conducted using the SAS system (SAS Institute Inc., Cary, NC) version 8.2.

results

Of the 5961 patients in these studies, 1717 patients (29%) lacked either CA15-3 or ALP measurements leaving 4244 patients who had both biomarkers measured at some time point (Figure 1). Analyses were on the basis of 3953 patients who had one or more measurements of both CA15-3 and ALP during their RFS period. The vast majority of patients had two or more consecutive CA15-3 measurements taken within 1 year, and over half of the patients had two or more consecutive measurements within 6 months. The analysis patients had 27341 CA15-3 values reported; 4196 (15%) values were abnormal, of which 2728 (65%) were >30 U/ml. Among the remaining 1468 abnormal values ≤30 U/ml (defined as abnormal on the basis of >50% increase from the first measurement), 66% were >15 U/ml. The first CA15-3 value was recorded at or within 1 year after randomization for 2649 analysis patients (67%), of whom 1183 (30%) had a value at their first follow-up visit (3 months after randomization). A total of 40440 ALP measurements were recorded, of which 935 (2%) were abnormal.

Breast cancer recurrence was reported for 784 (20%) patients included in the analysis. Table 2 gives the sites of first recurrence according to whether or not a patient had one or more abnormal CA15-3/ALP value during their RFS period. For both biomarkers, distant recurrences were much more frequent among patients with one or more abnormal biomarker value compared with patients who had only normal values (or normal and/or equivocal values for ALP). The frequency of distant recurrence in the bone and liver was particularly greater for patients with one or more abnormal ALP measurement. For both CA15-3 and ALP, the proportions of local, contralateral breast, and regional recurrences were similar (<5% difference) between patients with one or more abnormal biomarker and those with only normal values.

Figures 2 and 3 show the cumulative percentages of abnormal, normal (and/or equivocal for ALP), and missing biomarker

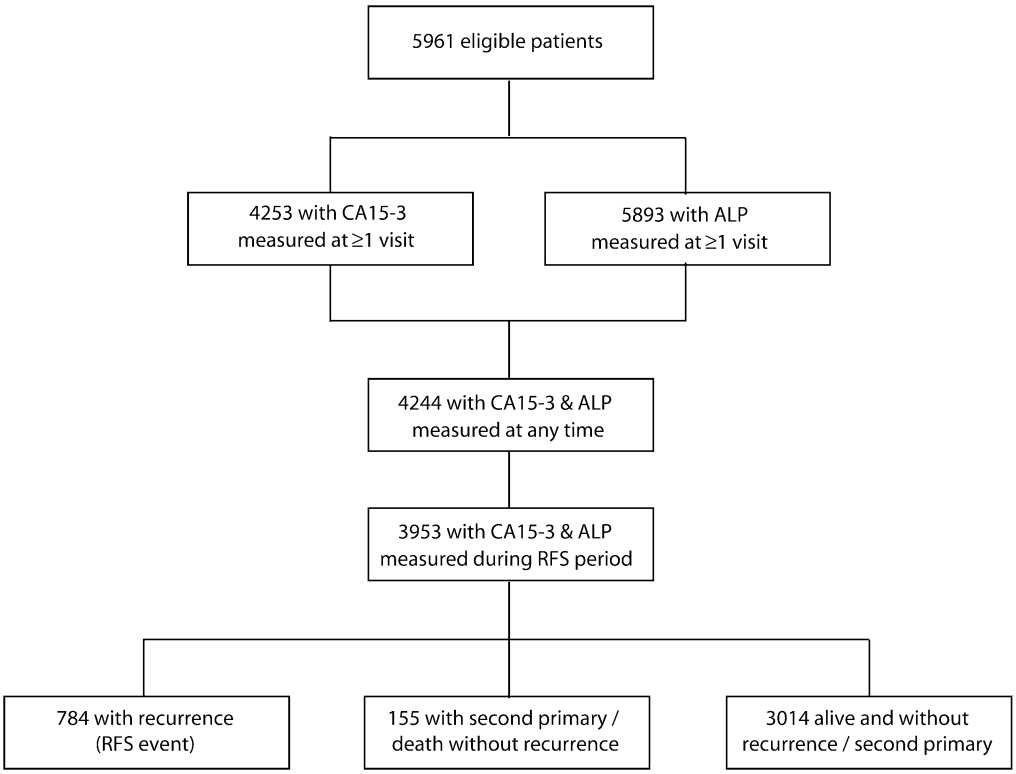

Figure 1. Patient population for primary analysis of relapse-free survival (RFS).

Table 2. Sites of first breast cancer recurrence amongst analysis population

Sites	Patients with zero abnormal CA15-3 values		Patients with one or more abnormal CA15-3 value		Patients with zero abnormal ALP measurements		Patients with one or more abnormal ALP measurement		Overall	
	N	%	N	%	N	%	N	%	N	%
Local	106	3.8	31	2.6	105	3.1	32	6.2	137	3.5
Contra breast	56	2.0	19	1.6	70	2.0	5	1.0	75	1.9
Regional ± above	51	1.8	20	1.7	51	1.5	20	3.9	71	1.8
Distant ± above	296	10.7	203	7.2	264	7.7	235	45.7	499	12.6
Soft tissue	16	0.6	6	0.5	12	0.4	10	2.0	22	0.6
Bone	103	3.7	73	6.2	92	2.7	84	16.3	176	4.5
Viscera	177	6.4	124	10.5	160	4.7	141	27.4	301	7.6
Liver	92	3.3	55	4.7	52	1.5	95	18.5	147	3.7
Nonliver	85	3.1	69	5.8	108	3.1	46	9.0	154	3.9
Unknown	1	<0.1	1	<0.1	1	<0.1	1	0.2	2	<0.1
Total events	510		274		491		293		784	
Total patients	2771		1182		3439		514		3953	

ALP, alkaline phosphatase.

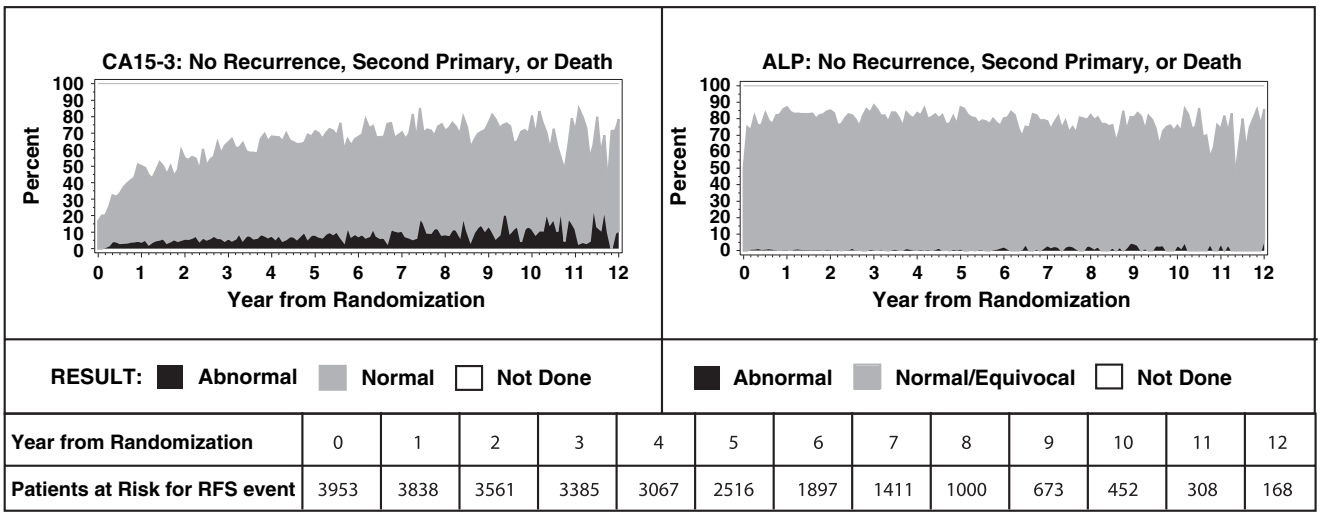

Figure 2. Patients without a recurrence, second (nonbreast) primary, or death (N = 3014). Percent of patients with abnormal, normal (and/or equivocal), and missing measurements over time, and number of patients at risk for a recurrence at the beginning of each year.

values over time for patients without and with an event, by end point. Of the 3014 patients alive and without a recurrence or second (nonbreast) primary, 929 patients (31%) had one or more abnormal CA15-3 value during their follow-up, and the percentage of patients with abnormal values was more or less constant over time (Figure 2). By comparison, of the 784 patients with a recurrence, 574 patients (73%) had one or more abnormal CA15-3 value at any time, while 274 (35%) had one or more abnormal CA15-3 value before recurrence. Beginning around 6 months before recurrence, the percentage of patients with an abnormal CA15-3 value increased (Figure 3, 1st column). For patients with a bone, liver, or nonliver visceral recurrence, the increase began even earlier, ~1 year before recurrence.

Since the measurement of ALP was a requirement in IBCSG trials, fewer patients had missing values at any given follow-up visit. Of the 3014 patients without a recurrence, 195 patients (6%) had one or more abnormal ALP measurement during their follow-up (Figure 2). By comparison, of the 784 patients with a recurrence, 293 patients (37%) had one or more abnormal ALP measurement at any time, while only 35 patients (4%) had one or more abnormal ALP measurement before recurrence. The pattern of abnormal ALP values over time was difficult to determine because so few patients had an abnormal measurement. Even so, an increase in the proportion of patients with abnormal ALP was seen ~1 month before recurrence, particularly in patients with a liver recurrence (Figure 3, 2nd column). The frequency of abnormal ALP did not greatly increase before a first bone or nonliver visceral recurrence.

Table 3 gives the results of the time-varying Cox model analyses for each end point. Abnormal CA15-3 value was associated with almost a two-fold increase in the risk of a recurrence ($P < 0.0001$), while abnormal ALP was associated

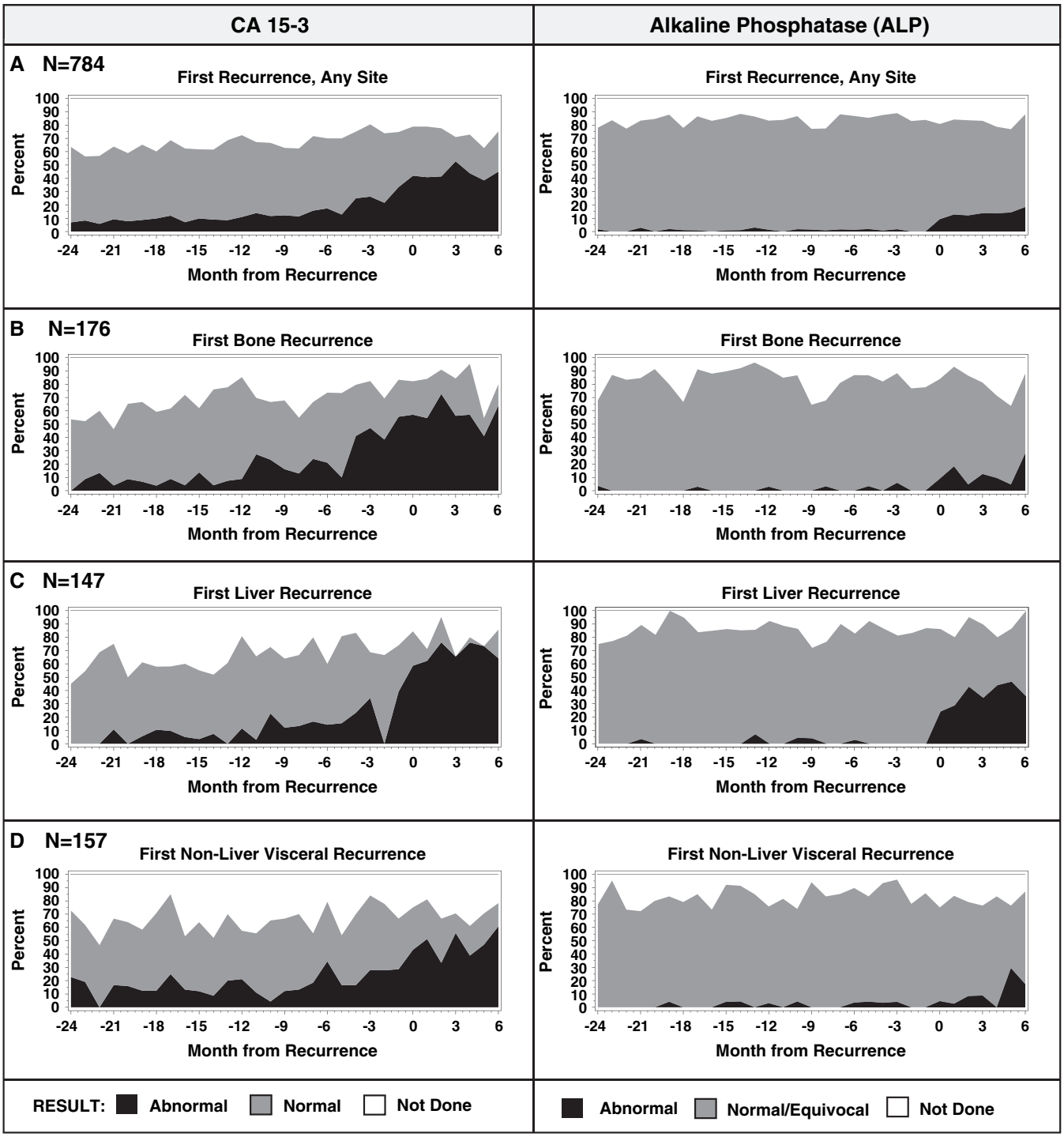

Figure 3. Percent of patients with abnormal, normal (and/or equivocal), and missing measurements over time by end point. First column is for analyses with CA15-3, and second column is for analyses with alkaline phosphatase (ALP).

with only a 4% increase in risk, which was not significant. The risk of bone, liver, and nonliver visceral recurrence were significantly increased for patients with abnormal CA15-3. The predictive value of ALP was greatest for liver recurrence, but was not significant for any site.

Time-varying Cox model analyses with both CA15-3 and ALP used in combination yielded greater predictive ability for RFS than either biomarker alone. The appearance of an abnormal value for either biomarker resulted in more than a three-fold increase in the risk of recurrence ($P < 0.0001$). The appearance of an abnormal value for both biomarkers resulted in more than a six-fold increase in the risk of a recurrence ($P < 0.0001$). For bone, nonliver visceral, and especially liver recurrence, the use of both biomarkers together (either abnormal and both abnormal) resulted in a greater ability than either marker alone to predict recurrence.

Table 3. Cox models analyses of CA15-3 and ALP, alone and together (N = 3953 patients)

Outcome	Patients (%) with one or more abnormal measurement	Cox model hazard ratio	95% confidence interval	Cox model *P*-value
Relapse-free survival (n = 784 events)				
CA15-3	1182 (30%)	1.97	(1.70, 2.28)	<0.0001
ALP	235 (6%)	1.04	(0.74, 1.46)	0.82
CA15-3 or ALP	1324 (33%)	3.31	(2.88, 3.82)	<0.0001
CA15-3 and ALP	93 (2%)	6.13	(5.05, 7.45)	<0.0001
Time to first recurrence: bone (n = 176 events)				
CA15-3	1354 (34%)	2.35	(1.74, 3.17)	<0.0001
ALP[a]	390 (9%)	0.71	(0.32, 1.61)	0.41
CA15-3 or ALP	1505 (38%)	4.86	(3.54, 6.68)	<0.0001
CA15-3 and ALP[a]	187 (5%)	6.58	(4.58, 9.46)	<0.0001
Time to first recurrence: liver (n = 147 events)				
CA15-3	1371 (35%)	2.29	(1.64, 3.19)	<0.0001
ALP[a]	340 (9%)	1.62	(0.85, 3.09)	0.14
CA15-3 or ALP	1520 (38%)	6.35	(4.40, 9.16)	<0.0001
CA15-3 and ALP[a]	191 (5%)	10.95	(7.72, 15.53)	<0.0001
Time to first recurrence: nonliver visceral (n = 154 events)				
CA15-3	1388 (35%)	2.86	(2.08, 3.94)	<0.0001
ALP[a]	371 (9%)	1.24	(0.63, 2.44)	0.53
CA15-3 or ALP	1540 (39%)	3.61	(2.61, 4.99)	<0.0001
CA15-3 and ALP[a]	219 (6%)	3.97	(2.55, 6.19)	<0.0001

[a]Results may be unstable, as it is on the basis of ≤10 patients with an event and one or more abnormal biomarker values.
ALP, alkaline phosphatase.

discussion

CA15-3 has been shown to be highly sensitive for distant metastases, especially in the bone and liver [29–31], but not sensitive for locoregional or contralateral breast cancer [32]. ALP has consistently been shown to predict bone metastases, and to some extent liver metastases, as expected on the basis of its biologic activity. While some studies have reported fairly high sensitivity of ALP for bone and overall metastases detection, these studies included the use of specific isoenzymes in addition to total ALP [33].

A challenge for this study of CA15-3 and ALP was the definition of abnormal. The IBCSG trials collected CA15-3 as a value, but there is currently no clear clinical cut-off for considering CA15-3 abnormal; cut-offs in other studies have varied from 22 to 60 U/ml [34, 12]. The choice of the cut-off to classify CA15-3 could indeed affect conclusions; a lower cut-off would likely decrease predictive value, while a higher cut-off may increase predictive value. For ALP, the IBCSG trials collected whether the marker was abnormal, normal, or equivocal (with normal and equivocal combined to make up the referent group), and no specific enzymes were measured.

The results of our analyses indicate that abnormal CA15-3 signals a significant increase in the risk of breast cancer recurrence. CA15-3 was a better predictor than ALP of recurrence in all sites examined. While ALP was not a significant predictor of recurrence, the analyses were likely underpowered, due to the low prevalence of abnormal ALP measurements (<10%).

When the biomarkers were used together the predictive value was greatest. Though ALP had an inferior predictive value than CA15-3, it increased predictive value when used with CA15-3, especially for liver recurrence. Thus, given it is a relatively inexpensive test to run, it is sensible to continue the use of ALP along with CA15-3 to monitor the risk of recurrence. Our findings support the results obtained by Buamah et al. [29], who found that predictive value of CA15-3 used in combination with carcinoembryonic antigen (CEA) (i.e. abnormal, defined as both biomarkers being abnormal) was augmented when ALP was also included. Ritzke et al. [33] found that, among breast cancer patients in the adjuvant setting, ALP isoenzymes in combination with CA15-3 led to the greatest sensitivity and positive predictive value (PPV) for bone metastases, while ALP isoenzymes in combination with CEA led to the greatest sensitivity and PPV for liver metastases. In our analysis, CA15-3 appeared to signal recurrence ∼5 months earlier than ALP, indicating that these markers may be yielding different information on the risk of a recurrence. This assertion is further supported by the fact that, at each follow-up visit, fewer than 15% of patients who had both biomarkers measured at that visit had both biomarkers abnormal.

We encourage caution in extrapolating these results to a general breast cancer population. Our analyses excluded patients who did not have CA15-3/ALP measured before the event of interest or last follow-up visit. Thus, very high risk patients who had a recurrence shortly after randomization were more likely to have missing biomarker measurements, and thus more likely to have been excluded from the analyses. Because CA15-3 was more frequently obtained for the more recently conducted trials, we found that the median follow-up and percentage of patients with recurrence was greater for patients with no CA15-3 values reported than for those who had one or more CA15-3 value reported at any time on the study.

By contrast, the median follow-up and percentage of patients with a recurrence was lower for patients with no ALP measurements than for those who had at least one ALP measurement. These findings show the change in practice of IBCSG investigators over the years (ALP was measured early on, but partially replaced over time by CA15-3), and challenge the generalizability of the results.

Furthermore, a high CA15-3 value may have stimulated the physicians to more aggressively order confirmatory tests for recurrence, compared with action taken for patients with negative CA15-3 or with no assessments at all. In this case, at least some of the effect observed would be due to CA15-3 increasing the chances that a recurrence was proven (and therefore counted as an event). However, we found that the percentage of patients with one or more CA15-3 measurement was similar among patients with and without recurrence, indicating that any differential bias was likely limited in magnitude.

Routine follow-up programs after primary therapy for early-stage breast cancer vary. In an era of increasing financial constraints, physicians are critically reevaluating various clinical practices that have not been shown to be cost-effective or associated with definitive patient benefit [35]. Our analyses show explicitly that the appearance of an abnormal CA15-3 and/or ALP measurement is associated with an increased risk of definitive recurrence. It is possible that early detection of overt distant metastases for patients who undergo proper local and systemic adjuvant therapy, however, does not provide a known benefit, as compared with reliance on detection of symptomatic disease [36–40]. Since our analysis focused only on predicting breast cancer recurrence, whether the routine use of these biomarkers improves OS remains an open question [3].

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